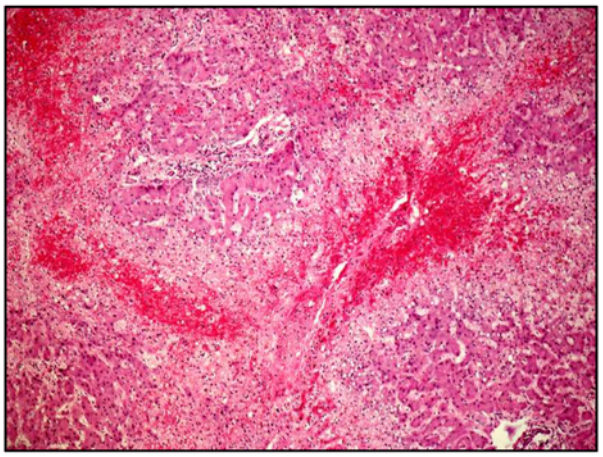
Post-Hepatic

- **Congestive Hepatopathy**
  - Etiology: constrictive pericarditis, RHF, pulmonary HTN, TR
  - Mechanism: hepatic congestion
  - Labs
    - mild abnl LFTs (mildly high INR (most common), mildly high TB (<3mg/dL), mildly high AP, rarely high AT)
  - S/S
    - RUQ pain 2/2 distension of Glissen's capsule and HM w/ HJ reflux and JVD
  - Dx
    - Ascites (high SAAG and high AFTP ascites)
    - TTE or Doppler TA-US (dilated hepatic vein and IVC)
    - CT (hepatomegaly w/ homogenous enhancement during the portal phase)
    - Bx (prominent central veins, dilated centrivenular sinusoids w/ surrounding atrophic/necrosed hepatocytes and hemorrhage)



    - Gross (enlarged/congested w/ prominent hepatic veins and "nutmeg" appearance on cut surface (lighter periportal areas surrounding darker perivenular area representing congestion/hemorrhage))
  - Complications
    - Cardiac Cirrhosis
      - unique vein-to-vein fibrosis and not portal-to-portal fibrosis seen in other types of cirrhosis
      - you must have both congestive hepatopathy AND mild ischemia 2/2 CHF (congestive hepatopathy alone cannot cause cirrhosis)
    - Interestingly does not affect the prognosis in pts w/ CHF!!!
  - Tx
    - improve cardiac function
    - TIPS is contraindicated b/c leads to high portal pressure and acute-CHF
    - avoid paracentesis b/c of the significant loss of protein b/c post-sinusoidal

Intra Hepatic Post Sinusoidal

- **Budd Chiari Syndrome (BCS)**
  - Mechanism: occlusion of LARGE hepatic outflow vessels (Hepatic Venules → Hepatic Veins → IVC → R Atrium)
  - Etiology
    - Thrombosis (Americas/Europe) typically proximally, more sub-acute
      - Thrombophilia (80%) esp Myeloproliferative Disorders
      - Idiopathic (10%)
      - Compressive Dz (rare) esp Malignancy, Infection (Hydatid Cyst, Abscess, TB, Aspergillosis)
      - Systemic Inflammation (rare) esp Behcet's, IBD, Sarcoidosis
    - Membranous Webs (Africa/Asia) typically distally, more chronic
      - Cause unknown, congenital as many seen in children but a second peak occurs during the 4th decade which may 2/2 chronic infection, higher r/o HCC
  - S/S
    - protean presentation depending on the acuity/extent of obstruction and the degree of collateral formation from acute symptomatic hepatitis to hepatic failure (important cause, classically seen in pregnant women w/ underlying thrombophilia, collaterals cannot form) vs chronic asymptomatic abnormal LFTs to cirrhosis (usually Sx are sub-acute over ~3-6mo, collateral have formed)

        - Classic Triad: Hepatomegaly + Ascites (high SAAG, high AFTP, protein rich fluids extravasate into ascitic fluid) + RUQ Ab Pain
        - Depends on the number/location/rapidity of veins affected
        - If IVC occlusion there is unique dilated SC veins over the back/flanks
        - LFTs are generally non-specific and variable but overall mild w/ TB <5mg/dL, AT<2xULN
    - Dx
        - Doppler US of Hepatic Veins and IVC (85% sensitive, obstruction or decreased flow w/ intrahepatic "spider-web" venous-to-venous collaterals, enlarged caudate vein), delayed venous phase CT/MR are complementary, TJ hepatic venography is reserved for pre-operative/catherative planning
        - Bx: heterogenous (false negatives b/c of sampling error), acute (centrilobular congestion → perivenular sinusoidal dilation and hemorrhage → necrosis w/ hepatocyte dropout) vs chronic (centrilobular fibrosis)
        - in acute dz there is generalized hepatomegaly but in chronic dz there is actually generalized atrophy (as the liver begins to cirrhosis) w/ caudate lobe hypertrophy (this is b/c the caudate lobe bypasses hepatic veins draining directly into IVC thus it hypertrophies over time as it compensates for a cirrhotic liver)
    - Tx
        - Chronic: anticoagulation and diuretics but most need an interventional Tx
        - Acute: AC, direct thrombolysis, if focal obstruction then stenting and/or angioplasty, if refractory or evidence of necrosis on Bx then TIPS or surgical shunting is generally used to stabilize function and bridge pts to transplant but can be used as a definitive Tx in some pts (close surveillance as TIPS occlusion is a common complication near 70%, more so than any other indication for TIPS, w/ the use of covered stents occlusion rates have dropped from 87% to 33% at 1yr) lastly transplant
        - Fulminant: transplant (5-yr survival rates are comparable in pts undergoing transplants for other reasons, in cases when the underlying thrombophilia is 2/2 protein C/S/AT-III deficiency transplantation is curative!!! Otherwise pts should receive life-long AC, recurrence is 5-10% at 5yrs, 5yr survival is at 85%)
        - NB for MPD the recommended Tx is hydroxyurea, ASA, and anegrilide NOT AC or lytics
- **Sinusoidal Obstruction Syndrome (SOS) formerly called Veno Occlusive Disease (VOD)**
    - Mechanism: depolymerization of F-actin in centrilobular sinusoidal endothelial cells → dissection of the sinusoidal lining off the space of Disse → this injury continues distally into terminal venule → embolization of cellular debris, exfoliated cells, extravasated RBCs, activated coagulation factors (controversial, most consider SOS to be a non-thrombotic unlike Budd-Chiari but recent evidence suggests that hemostatic abnormalities may be present specifically low protein C) → progressive occlusion of SMALL hepatic outflow vessels (Sinusoids → Hepatic Venules) → fibrosis over time
    - Etiology
        - Fibro-Obliterative Endophlebitis
            - Bone Marrow Transplantation (US, more acute presentation)
                - Occurs w/in 30d of transplantation
                - RFs: high dose immunosuppressants (Busulfan, Cyclophosphamide, Thiotepa), HCV, Allogeneic Transplant, pre-Tx abnl LFTs, low Protein C activity, hepatic irradiation
                - Incidence: 4.7-5.3%
                - Prognosis: <20% die
                - Generally more acute presentation
                - Tx: Heparin, Defibrotide → TIPS → Transplant
                - Must differentiate from GVHD, Sepsis, Drug Toxicity
                - NB there have also been cases of SOS in pts on long-term azathioprine (eg. renal/liver transplants, IBD)
            - Pyrrolizidine Alkaloids Ingestion (non-US, more chronic presentation)
                - First described in South Africa in 1920 (Willmot, 1920) after an epidemic of liver failure w/ *Senecio* ingestion
                - Well characterized in Jamaica in 1954 when the toxin, pyrrolizidine alkaloid, was found to be the toxic agent
                - Recent established epidemics in Jamaica, India, Egypt, Iraq, South Africa and represents the most common of SOS in the world
                - Ingested either un-intentionally from contaminated food or when PA-containing plants are misused for medical purposes including arthritis, gout, diarrhea
                - Common preparation: steeped into a "bush tea", occasionally unintentional ingestion from contamination of honey, milk, eggs has been reported
                - PAs comprises a group of >305 natural toxins which share the basic structure of two linked pyrrole rings
                - PA has been identified in >6000 plant species (3% of flowering plants) belonging to the three families (*Boraginaceae, Asteracea, Fabacea*) each w/ widely varying concentrations of PA, toxin is usually concentrated at the root (little in leaves and flowers)
                - Acute intoxication can lead to hemorrhagic necrosis vs chronic intoxication (SOS, biliary tract hypertrophy, steatosis, along w/ lung injury)
                - PAs have little toxicity in their native form, they become toxic when they are actually modified by CYP3A4 hence the unique damage to Zone 3 (primary location for the P450 system)

- Other
    - Hypervitaminosis A
    - Arsenic Poisoning
    - Insecticide Exposure
    - Thorotrast Exposure
    - OCPs
    - Chemo (actinmycin, mithramycin, dacarbazine, cytosine analogues)
- S/S: similar to BCS
- Dx: can only be made by liver bx b/c the vessels affected are very small and thus cannot be visualized on imaging (may see hepatomegaly, ascites, attenuated hepatic flow on US) but most cases are clinical diagnoses
    - Bx: venular subendothelial injury→ perivenular/centrilobular sinusoidal dilatation w/ RBC extravasation → perivenular hepatocyte necrosis (NB inflammation is notably absent but eventually sclerosis ensues resulting in a fixed obstruction)
- Tx
    - no definitive Tx
    - most cases are mild and do well w/ conservative supportive care including (diuretics, analgesics, paracentesis, avoidance of hepatoxins)
    - Meds Previously Studied: Glucocorticoids, tPA, NAC, Antithrombin III, Protein C (results are inclusive)
    - Current Med Under Investigation: Defibrotide (oligodeoxyribonucleotide w/ anti-ischemic, anti-thrombotic, thrombolytic activity)
    - TIPS (poor results, 50% show clinical improvement but only 10% survive long term)
    - Transplant (has been performed successfully but in the US where the primary causes is s/p BMT most pts are not candidates)
- Px
    - recognize RFs b/f BMT and altering chemo regimens/doses
    - studies have looked at URSO, AC (heparins, tPA), anti-inflammatories (methylprednisolone, pentoxyflline, prostaglandin E1) but results are not conclusive
- Prognosis: variable depending on severity and presence of other organ damage w/ near 00% mortality when considered severe

Intra Hepatic Sinusoidal

- **Cavernous Hepatic Hemangioma, Infantile Hemangioendothelioma, Hemangiosarcoma, Epithelioid Hemangioendothelioma (refer)**
- **Peliosis Hepatis**
    - Mech: multiple blood filled 0.1-3cm cysts throughout the liver lined by hepatocytes or endothelium
    - Etiology: immunosuppressed pts infected w/ *Bartonella henselae* = "Bacillary Peliosis Hepatis" (refer), medication exposure (s/p kidney transplant on prolonged azathioprine/cyclosporine, anabolic steroids, OCPs, VitA, vinyl chloride), unusual diseases (agnogenic myeloid metaplasia, malignant histiocytosis, Castelman's disease)
    - S/S: asymptomatic abnormal LFTs to acute hepatitis
    - Dx: if large enough they can be seen on imaging
    - Tx: abx, medication cessation, treatment of the underlying disorder

Intra Hepatic Pre Sinusoidal

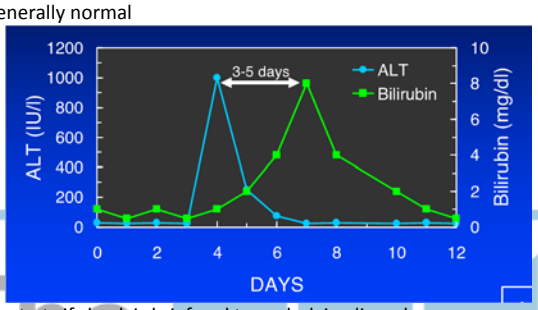
- **Schistosomiasis**
    - eggs deposit in pre-sinusoidal venules resulting in a granulomatous inflammatory response resulting in "clay pipestem" fibrosis, most common cause of portal HTN world-wide!!!

Pre-Hepatic

- **Arteriovenous Fistula**
    - splanchnic artery ruptures into a mesenteric vein creating a fistula (bruit) and subsequent acute increase in portal pressure resulting in acute ascites and variceal bleeding
- **Osler-Weber-Rendu Syndrome aka Hereditary Hemorrhagic Telengiectasia**
    - AD mutation (+FHx in 80% of pts) of various proteins (esp endoglin, activin receptor like kinase, et al) involved in angiogenesis
    - Skin/mucosal telengectasias of skin (esp hand/fingers/nails/nose/lips and conjuctiva and pharynx resulting in epistaxis - usually the presenting Sx during first few years of life)
    - AVMs in GI organs (mainly UGI esp stomach/SI but sometimes LGI w/ GIB and also liver (8-30%) w/ arterioportal shunts esp hepatic artery and portal vein, arteriosystemic shunts, telengiectasias, vascular masses)
        - in general screening is not needed b/c most remain asymptomatic and do not need Tx
        - if symptomatic then they p/w high CHF and cholestasis from ischemia to biliary tree from arteriovenous shunt, portal HTN from arterioportal shunt, HE from portosystemic shunt → Tx (embolization to transplantation)
- **Hepatic Artery Aneurysm**
    - Visceral Artery Aneurysms: 1° Splenic, 2° Hepatic
    - Etiology: atherosclerosis, s/p trauma (liver bx, surgery, transplant), mediointimal degeneration, trauma, infection aka mycotic, vasculitis, CTD
    - S/S: asymptomatic, RUQ pain w/ pulsatile mass, rupture into biliary tree / portal vein / peritoneum

- Tx: embolization vs surgery esp if >2cm, multiple, non-atherosclerotic

- **Ischemic Hepatitis aka "Shock Liver"**
  - Etiology: HA thrombosis, HA damage during surgery, HA embolization during TACE, vasculitis, sepsis, hemorrhage, severe burns, CHF, MI, PE, heat stroke
  - S/S: sometimes hypotension is not clinical evident, other concurrent organ including ATN, pts are generally very sick in the ICU from the underlying cause thus liver S/S are not apparent
    - Outcome depends on restoration of hepatic blood flow
      - Transient (eg. brief shock) = rapid recovery w/ no long term effects
      - Permanent (eg. severe MI, underlying PVT) = no recovery w/ ALF or cirrhosis and ischemic cholangiopathy
  - Bx shows perivenular (Zone 3) necrosis, rare inflammatory infiltrates (really shouldn't be called a hepatitis)
  - Labs: VERY IMPORTANT PATTERN WITH TWO WAVES
    - (1) acute transaminasemia in the ~1000 (also LDH very high) w/ quick peak at ~4d and quick normalization at ~6d (quick rise and fall is characteristic of ischemia unlike any other cause of acute severe transaminitis
    - (2) TB begins to rise AFTER transaminasemia and quickly peaks at ~6d with gradual normalization at ~12d
    - NB INR/AP remains generally normal



  - Histology returns to normal in most pts if shock is brief and to underlying liver dz
  - Always r/o viral, toxin, DILI, autoimmune
  - Tx: supportive as transient and self-limited, fulminant failure is uncommon but may occur if underlying liver disease
    - NB there were some studies looking at low dose dopamine and adenosine to augment hepatic blood flow but data is poor
  - Complication: hepatic infarction usually affecting one segment therefore global function is only marginally impaired, generally more symptomatic w/ more impressive labs, wedged shaped on imaging, r/o infection of the infracted tissue, ischemic cholangiopathy
  - Tx: if large the r/o infection/abscess is high, fulminant liver failure can result requiring transplant, seen as complete necrosis, can occur following severe shock liver, hepatic artery damage during surgery (transplantation, chole, etc), TIPS placement, administration of IA chemo or embolization for Tx of HCC, septic emboli, SCD crisis, thrombosis, aortic dissection
- **Ischemic Cholangiopathy**
  - Etiology: any GB/Biliary/Hepatic surgery
  - Sensitive b/c bile ducts receive their blood supply from small cystic? branches of the hepatic artery
  - S/S: single short smooth biliary stricture
  - Tx: stent or surgical revision
- **Hepatic Artery Thrombosis (post-transplant complication)**
- **Portal Vein Thrombosis**
  - Etiology (NB 25% of cases are idiopathic but most of these pts end up having a hypercoagulable dz, 40% of pts have multiple causes)
    - Local (30%)
      - Cirrhosis esp with HCC invasion (suggestive when portal vein is >23mm, endoluminal material enhances w/ contrast or when there is arterial pulsatile flow), also consider when a cirrhotic pt decompensates, increased risk the worse the cirrhosis (1% of compensated cirrhotics vs 8-25% of cirrhotics on Tx list)
      - Any GI Cancer not just when there is invasion/constriction but also if cancer is near venous territory
      - Any GI Inflammation esp pancreatitis, cholecystitis, diverticulitis, IBD, appendicitis, cholangitis
      - Injury to Portal Vein esp during splenectomy, colectomy, gastrectomy, liver transplant, portosystemic shunt
      - Omphalitis leading to umbilical vein and ultimately portal vein thrombosis which can exist into adulthood
    - Distant (70%)
      - Hypercoagulable State
      - Myeoproliferative Disease
    - NB isolated splenic vein thrombus is usually with pancreatic disease and characterized by the presence of gastric varices
  - Types
    - Acute

- Usually asymptomatic but if symptomatic then non-specific ab pain, bowel edema/ischemia and bacteremia
- LFTs are generally nl b/c 2/3 of oxygen comes from hepatic artery

- Chronic
  - Usually asymptomatic but if symptomatic then portal HTN S/S but typically a unique pattern:
  - ectopic varices (duodenal, gallbladder, rectum)
  - ascites is RARE b/c the obstruction is post-sinusoidal
  - LFTs are generally nl
  - Often "cavernous transformation" occurs in which the portal vein is replaced by collaterals in the porta hepatis recreating normal hepatopetal flow, NB these varices can actually compress the biliary tract causing "portal biliopathy/cholangiopathy"

- Tx: prevent/Tx GIB and always screen pts w/ EGD for varices +/- AC
  - No AC
    - Cirrhosis
  - Possible AC
    - Chronic PVT from Hypercoagulable State (use of AC is very controversial (good: prevent further clotting vs bad: risk of bleeding) hence it is given if no cirrhosis and pt is in a permanent thrombophilic state and there are no varices, Tx portal biliopathy/cholangiopathy if present w/ stent, if splenic vein thrombosis then splenectomy)
    - Asymptomatic Acute PVT
  - Definite AC
    - Symptomatic Acute PVT
      - 50/40/10% complete/partial/no recanulization rates at 6mo
      - spontaneous recanulization is rare
      - Tx for 3-6mo or chronic if thrombophilia or recurrent symptomatic acute PVT
      - thrombectomy or lytics is reserved for cases in which thrombosis extends into the SMV resulting in impending intestinal ischemia
- Complications
  - phlebitis (infected thrombus)
  - provided there is no extension into mesenteric venous system (which causes ischemia) PVT does not cause ischemia to other organs and in general ischemic injury to the liver is very rare
  - left liver lobe atrophy
- Prognosis
  - Survival depends on underlying liver dz
  - 2% experience fatal EV bleed (NB EV bleeds for PVT have much better outcome than that observed w/ EV bleeds caused by cirrhosis b/c of preserved hepatic function and lack of coagulopathy)
- Dx
  - LFTs (generally normal even though portal blood flow to liver is decreased the hepatic artery can compensate)
  - US (hyperechoic thrombus in the vessel w/ extensive collaterals in the porta hepatis and splenomegaly) w/ Doppler (absent flow)
  - CT (if US not conclusive)